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Prenatal Exposure to Air Pollution and Respiratory Distress in Term Newborns: Results from the MIREC Prospective Pregnancy Cohort

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Background: Respiratory distress is the leading cause of neonatal morbidity and mortality worldwide, and prenatal exposure to air pollution is associated with adverse long-term respiratory outcomes; however, the impact of prenatal air pollution exposure on neonatal respiratory distress has not been well studied.

Objectives: We examined associations between prenatal exposures to fine particular matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) with respiratory distress and related neonatal outcomes.

Methods: We used data from the Maternal–Infant Research on Environmental Chemicals (MIREC) Study, a prospective pregnancy cohort ($n = 2{,}001$) recruited in the first trimester from 10 Canadian cities. Prenatal exposures to $PM_{2.5}$ ($n = 1{,}321$) and NO_2 ($n = 1{,}064$) were estimated using land-use regression and satellite-derived models coupled with ground-level monitoring and linked to participants based on residential location at birth. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) for associations between air pollution and physician-diagnosed respiratory distress in term neonates in hierarchical logistic regression models adjusting for detailed maternal and infant covariates.

Results: Approximately 7% of newborns experienced respiratory distress. Neonates received clinical interventions including oxygen therapy (6%), assisted ventilation (2%), and systemic antibiotics (3%). Two percent received multiple interventions and 4% were admitted to the neonatal intensive care unit (NICU). Median $PM_{2.5}$ and NO_2 concentrations during pregnancy were 8.81 $\mu g/m^3$ and 18.02 ppb, respectively. Prenatal exposures to air pollution were not associated with physician-diagnosed respiratory distress, oxygen therapy, or NICU admissions. However, $PM_{2.5}$ exposures were strongly associated with assisted ventilation (OR per 1-$\mu g/m^3$ increase in $PM_{2.5} = 1.17$; 95% CI: 1.02, 1.35), multiple clinical interventions (OR per 1-$\mu g/m^3$ increase in $PM_{2.5} = 1.16$; 95% CI: 1.07, 1.26), and systemic antibiotics, (OR per 1-$\mu g/m^3$ increase in $PM_{2.5} = 1.12$; 95% CI: 1.04, 1.21). These associations were consistent across exposure periods—that is, during prepregnancy, individual trimesters, and total pregnancy—and robust to model specification. NO_2 exposure was associated with administration of systemic antibiotics (OR per 1-ppb increase in $NO_2 = 1.03$; 95% CI: 1.00, 1.06).

Discussion: Prenatal exposures to $PM_{2.5}$ increased the risk of severe respiratory distress among term newborns. These findings support the development and prioritization of public health and prenatal care strategies to increase awareness and minimize prenatal exposures to air pollution. https://doi.org/10.1289/EHP12880

Introduction

The human health impacts of air pollution have been well documented.[1–3] The Global Burden of Disease initiative identified ambient air pollution as a leading cause of global mortality and disability-adjusted life years, with a global burden of >4 million premature deaths annually attributable to ambient air pollution that is mainly due to cardiovascular and respiratory morbidity and mortality, as well as health impacts associated with adverse birth outcomes.[1,4]

Extensive evidence links air pollution with adverse respiratory health outcomes across the life span.[2,5–9] In addition, a growing body of research highlights the importance of early life exposures to air pollution on immunologic[10] and pulmonary development,[6,7,11–13] with previous research suggesting that fetuses are particularly vulnerable to environmental exposures and that *in utero* exposures to environmental stressors may be associated with abnormal developmental pathways.[12–14] Exposure to air pollution during pregnancy has been linked with an increased risk for adverse birth outcomes, such as preterm birth, intrauterine growth restriction (IUGR), small for gestational age (SGA), and low birth weight (LBW), as well as neurocognitive disorders[15] and birth defects.[10,16–22] This is significant because prematurity and IUGR have been associated with short- and long-term adverse respiratory outcomes, including neonatal respiratory distress,[23,24] abnormal lung development,[25,26] and asthma.[27–30] Prenatal exposures to air pollution have also been directly linked to adverse respiratory outcomes in childhood and adulthood, including, but not limited to, the development of asthma,[12,30,31] allergic rhinitis,[32] chronic obstructive pulmonary disease,[29] as well as reduced pulmonary function[26,33] and increased incidence and severity of respiratory infections.[21,34] These findings suggest that *in utero* exposure to air pollution-mediated growth deficits are part of a continuum that may promote the development of adverse respiratory outcomes later in life.

Despite the growing weight of evidence demonstrating associations between prenatal air pollution exposure and long-term adverse respiratory outcomes, the impact of prenatal air pollution exposure on neonatal respiratory distress is not well studied. Neonatal respiratory distress is the leading cause of early neonatal mortality worldwide and a major contributor to neonatal hospitalizations and neonatal intensive care unit (NICU) admissions.[35,36] In addition, the use of assisted ventilation[37,38] and oxygen therapy[38] in neonates has been associated with adverse long-term respiratory outcomes,[37] associations that have persisted despite advances in

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ventilation strategies.[39] To the best of our knowledge, only one previous study has examined the potential impact of air pollution on this outcome.[40] To address this critical research gap, we used detailed clinical, sociodemographic, and behavioral information from the Maternal–Infant Research on Environmental Chemicals (MIREC) Study combined with fine-scale air pollution models to examine associations between air pollution and respiratory distress in full-term neonates.

Methods

Study Population

We analyzed data from the MIREC Study, a prospective cohort of pregnant women recruited in the first trimester between 2008 and 2011.[41] The details of the study design have been published elsewhere.[41] Briefly, 2,001 pregnant women were recruited from 10 Canadian cities (Vancouver, Edmonton, Winnipeg, Sudbury, Hamilton, Toronto, Kingston, Ottawa, Montreal, and Halifax). Recruitment was conducted at urban prenatal clinics during the first trimester of pregnancy (6 to <14 wk of gestation). Participants were excluded from the MIREC Study if they had a serious medical condition, known fetal chromosomal or congenital anomalies, were <18 years of age, were at >14 wk gestation at the time of recruitment, or could not communicate in either English or French. All participants completed baseline and follow-up questionnaires in each trimester to collect sociodemographic and exposure information. Clinical data were extracted from medical records.

The MIREC Study was approved by the research ethics boards (REBs) of Health Canada, Hospital Sainte Justine, and each of the MIREC Study sites. The analyses reported in this paper were approved by Health Canada's REB, the MIREC Biobank, and the institutional review board of Pennsylvania State University. Informed consent was obtained from all participants. Although pregnant people may identify as male or female, gender was not collected in the original MIREC Study. For the sake of clarity, we refer to pregnant participants and delivering parents in this paper using the terms "women," "mother," and "maternal."

Air Pollution Exposure

We examined average exposures to fine particulate matter [PM ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$)] and nitrogen dioxide (NO_2) during the 3 months prior to pregnancy (trimester 0) and individual trimesters (trimesters 1, 2, and 3), as well as average exposures during pregnancy (trimesters 1–3) and prepregnancy plus pregnancy (trimesters 0–3). The air pollution models and methods for determining prenatal exposure histories have been described elsewhere.[42] Briefly, we derived surface-based $PM_{2.5}$ estimates with a spatial resolution of 1×1 km from a combination of satellite estimates, chemical transport modeling, and geographically weighted regression.[43] We derived ambient NO_2 concentrations from a national land-use regression model that included land-use characteristics and satellite data with a spatial resolution of <100 m.[44] These data have been used extensively in previous epidemiological studies.[10,42,45–48] As described in previous analyses,[40] air pollution exposures were linked to each participant based on their forward sortation area (FSA), representing maternal residential location at birth. Canadian FSAs comprise the first three characters of the Canadian postal code and can range from very small sizes in urban areas ($<2 \times 2$ km) to large sizes in rural areas ($>40 \times 40$ km). However, participants living in large FSAs ($>20 \times 20$ km) were excluded to reduce exposure misclassification. FSAs were provided during the first and third trimester visits.

We added temporal resolution for both $PM_{2.5}$ and NO_2 using ground-level measurements from the National Air Pollution Surveillance (NAPS) monitoring stations located within 30 km of each FSA.[42] Participants living >30 km from a NAPS monitoring station were excluded from the analyses. Daily pollution estimates were obtained by combining long-term concentrations derived from satellite and land-use regression modeling with mean daily measurements from NAPS monitoring sites within 30 km of each participant's FSA centroid, as described previously.[42] Average concentrations for each exposure period (e.g., prepregnancy, individual trimesters, pregnancy averages) were calculated as the arithmetic mean of daily concentrations within each exposure period. We excluded participants who were missing >25% of their daily air pollution data during the study period. This approach has been used to estimate exposure in previous MIREC analyses linking air pollution with inflammatory biomarkers[10] and birth weight (BW).[42]

Neonatal Outcomes

The primary outcomes of the present study were neonatal respiratory distress and indicators of respiratory distress severity following birth. Respiratory distress was classified solely based on a physician diagnosis recorded in the medical record and reviewed by the study nurse after discharge from the delivery hospital; we did not classify respiratory distress indirectly, that is, based on receiving interventions, such as oxygen therapy, or International Classification of Diseases (ICD) codes. Respiratory distress was modeled as a dichotomous outcome (yes vs. no).

We also examined clinical interventions related to respiratory distress, including the use of oxygen therapy (yes/no), assisted ventilation (yes/no), and systemic antibiotics (yes/no). Indicators of severe neonatal respiratory distress included assisted ventilation or receiving multiple (two or more) interventions. None of the neonates received both oxygen therapy and systemic antibiotics without also receiving assisted ventilation; therefore, multiple interventions (yes/no) refers to neonates who received oxygen therapy with either both assisted ventilation and systemic antibiotics or at least one of them. Other outcomes (identified *a priori*) included admission to the NICU (yes/no), admission to an intermediate care unit (yes/no), and Apgar scores (good, ≥7, and low, ≤3) at 1 or 5 min following delivery,[49] both modeled as dichotomous outcomes (yes/no).

Maternal and Infant Covariates

Maternal and infant covariates considered in these analyses have been discussed in depth previously.[42] Briefly, sociodemographic and behavioral factors were assessed via maternal questionnaires administered during trimesters 1 and 3 of pregnancy. Maternal covariates included age (≤24, 25–29, 30–34, ≥35 y), parity (primiparous vs. multiparous), prepregnancy body mass index (BMI, in kilograms per meter squared; underweight, <18.5; normal, ≥18.5 and <25; overweight, ≥25 and <30; obese, ≥30), race/ethnicity (White vs. non-White), household income (<Can$ 50,000 vs. ≥Can$ 50,000), education (undergraduate university degree vs. less), and marital status (married or long-term partner >1 y; yes vs. no), as well as alcohol consumption and smoking during pregnancy (yes vs. no). We collapsed the detailed self-reported categories of race/ethnicity into White vs. non-White because of lack of sufficient sample size to differentiate between racialized subgroups. Finally, owing to the inverse association between FSA size and urbanicity, we considered FSA size (in kilometers squared) as a surrogate for urbanicity in some models. Infant covariates included infant sex, mode of delivery (vaginal vs. cesarean delivery, i.e., C-section), and season of delivery [warm (April–September) vs. cold months (October–March)]. Covariates were considered as potential confounders or effect modifiers based on

their relationships with respiratory distress in term neonates in the literature.[35,50]

Infant Growth and Gestational Age

Infant growth measures such as SGA, BW, LBW (defined as <2,500 g), and gestational age [early term (37–38 wk), full term (39–40 wk), and late term (41–42 wk)] were examined as potential effect modifiers and through sensitivity analyses.[51] Because of the small number of post-term infants born at 42 wk ($n = 6$), we combined them with the late-term infants. Infant growth measures and gestational age were not included as confounders because they may be part of the causal pathways between air pollution and adverse neonatal outcomes. Analyses examining fetal growth measures and gestational age are discussed in detail in the "Statistical Analyses" section below.

Maternal Health Problems and Pregnancy Complications

We also considered maternal health problems during and prior to pregnancy as potential effect modifiers. Prepregnancy health problems included *a*) any chronic health problems, *b*) metabolic disorders (diabetes, hypertension, and overweight or obese), *c*) diabetes or hypertension, and *d*) asthma. Overweight and obese were based on prepregnancy BMI; other health problems were self-reported. Maternal health problems during pregnancy included *a*) metabolic disorders (gestational hypertension, preeclampsia, impaired glucose tolerance, or gestation diabetes), *b*) any hospitalization during pregnancy, *c*) extended hospitalization during pregnancy (more than once or for >1 d), *d*) acute health problems during pregnancy, and *e*) any pregnancy complications (e.g., excessive vomiting and weight loss, vaginal bleeding, and other). Metabolic disorders and hospitalization during pregnancy were based on medical record review after delivery. Acute health problems during pregnancy and pregnancy complications were self-reported by participants during trimester 3.

Exclusion Criteria

Participants with multiple births were excluded. In addition, premature deliveries (before 37 wk of gestation) without multiple births were also excluded because premature and nonsingleton neonates are at increased risk for respiratory distress.[36] Participants without complete exposure and covariate data were also excluded. Starting with 1,983 MIREC participants, the analyses reported in this paper were restricted to live, singleton, full-term births ($n = 1{,}738$) and mother–baby pairs with complete sociodemographic, behavioral, and residential (FSA) information ($n = 1{,}501$). As discussed previously, we excluded participants living in large ($>20 \times 20$ km) FSAs ($n = 39$) from the analyses to reduce potential exposure misclassification. Of the remaining 1,462 participants, we limited the analyses to mother–baby pairs with at least 75% of daily air pollution values during pregnancy and prepregnancy periods. There were more missing values for NO_2, primarily owing to the lower density of NAPS monitoring stations measuring NO_2 during the study period. Exclusions are described in detail in Figure 1. A total of 1,321 and 1,064 mother–baby pairs were included in the analyses for $PM_{2.5}$ and NO_2, respectively.

Statistical Analysis

Associations between exposure to air pollution ($PM_{2.5}$ and NO_2) and neonatal health outcomes were examined using hierarchical logistic regression models. Odds ratios (ORs) relating pollutant exposures with neonatal outcomes were expressed per unit increase in the pollutant of interest (1-$\mu g/m^3$ $PM_{2.5}$ or 1-ppb NO_2). MIREC center—which represented the delivery hospital for most participants (or affiliated hospital for expected home births), as well as the

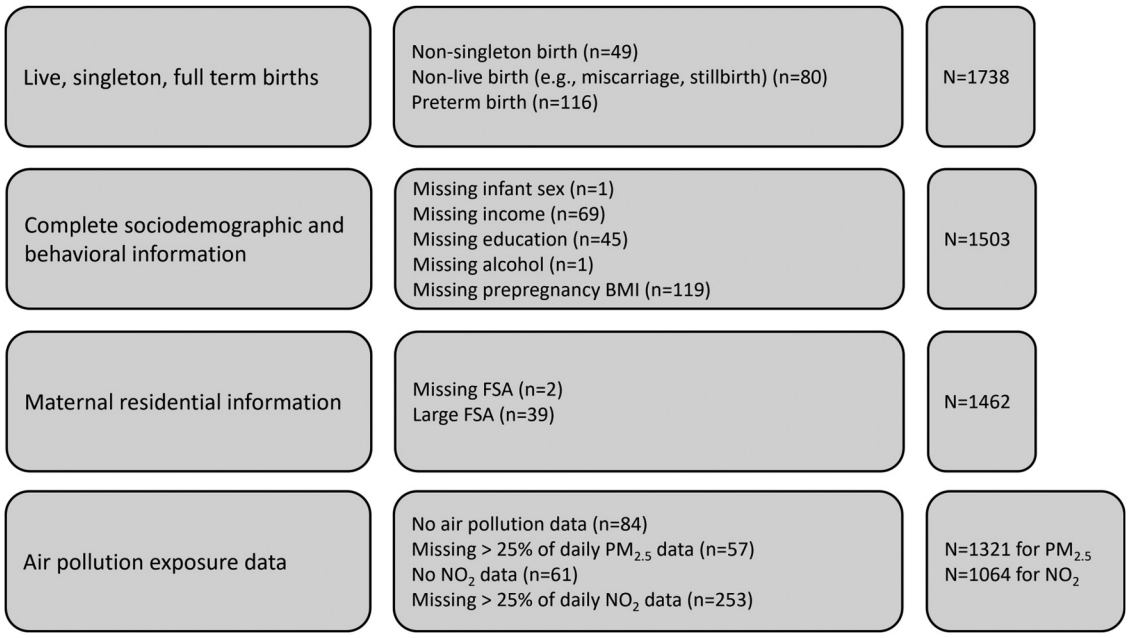

Figure 1. Study flow chart. From left to right: inclusion criteria, exclusions, and sample size. Figure 1 is a flow chart depicting the selection of study participants from the MIREC cohort ($n = 2{,}001$) in 4 steps. In Step 1, 49 non-singleton births, 80 non-live births (e.g., miscarriage, stillbirth), and 116 preterm births were excluded, resulting in 1,738 participants with live, singleton, full-term births. Step 2 further excluded 1 participant with missing infant sex, 69 missing income, 45 missing education, 1 missing alcohol exposure, and 119 missing prepregnancy body mass index, resulting in 1,503 participants with complete sociodemographic and behavioral information. In Step 3, 2 participants with missing Forward Sortation Area (FSA) and 39 with large FSA's were excluded, resulting in 1,462 participants with complete and usable maternal residential information. Step 4 excluded 84 participants with no air pollution data from all analyses, as well as 57 missing over 25% of daily fine particulate matter ($PM_{2.5}$) data from $PM_{2.5}$ analyses; 61 participants with no nitrogen dioxide (NO_2) data, and 253 missing over 25% of daily NO_2 data were excluded from NO_2 analyses, leaving a final sample size of 1,321 for $PM_{2.5}$ analyses and 1,064 for NO_2 analyses.

city of residence—was specified as a random effect. Maternal and infant covariates were specified as fixed effects. An independent correlation structure was identified as the best fit based on Quasi-likelihood under the Independence model information Criterion (QIC) testing.

We examined a broad range of potential predictors based on factors associated with neonatal respiratory distress and other adverse birth outcomes in the literature. These covariates are described in a directed acyclic graph for the direct effect of ambient air pollution exposure on neonatal respiratory distress (Figure 2). To specify parsimonious models, we narrowed the covariates included in the models as follows. Potential covariates were selected for inclusion in model 1 if they were associated ($p \leq 0.20$) with the outcome of interest or the pollutant of interest in unadjusted hierarchical linear regression models. In model 2, we also adjusted for FSA size, a surrogate for urbanicity, in addition to the covariates included in model 1. Covariates included in the models are detailed in Table 1.

We considered the impact of fetal growth indicators (SGA, BW, and LBW) on our results in several ways. We examined potential associations between fetal growth and neonatal health outcomes using analysis of variance (ANOVA) analyses and unadjusted hierarchical models; based on those results, we conducted sensitivity analyses excluding LBW and SGA neonates from the models. We also examined multiplicative interactions between fetal growth measures and air pollution in adjusted hierarchical models; however, these models did not converge owing to the small number of LBW and SGA infants in our analyses.

To examine the impact of gestational age, we conducted ANOVA analyses as well as partially stratified interaction models in which each gestational age category (early, full, and late) was coded as a binary variable and used to create a multiplicative interaction term with the air pollution exposure of interest. Gestational age interaction models included multiplicative interaction terms for exposure and each gestational age category and were adjusted for each gestational age category as well as the exposure of interest; but were otherwise identical to model 2.

Partially stratified GA interaction models:

$$\text{Neonatal health outcome} = \text{early term} \times \text{exposure} + \text{full\_term} \times \text{exposure} + \text{late\_term} \times \text{exposure} + \text{exposure} + \text{early\_term} + \text{full\_term} + \text{late\_term} + \text{covariates}$$

Finally, we examined potential interactions between maternal health problems and exposure using multiplicative interactions between binary maternal health variables and continuous air pollution exposures.

Maternal health and pregnancy complication interaction models:

$$\text{Neonatal healthoutcome} = \text{maternal health} \times \text{exposure} + \text{exposure} + \text{maternal health} + \text{covariates}$$

We conducted several other sensitivity analyses to test the robustness of our findings. To determine whether results were influenced by differences in late vs. early onset respiratory distress, we examined models limiting respiratory distress to early cases, detected within 4 h of delivery. We also conducted sensitivity analyses to determine whether associations between air pollution and NICU admissions were stronger when limited to neonates with respiratory distress. Finally, 7.9% and 8.3% of MIREC participants in $PM_{2.5}$ analyses ($n = 1{,}321$) and NO_2 analyses ($n = 1{,}064$), respectively,

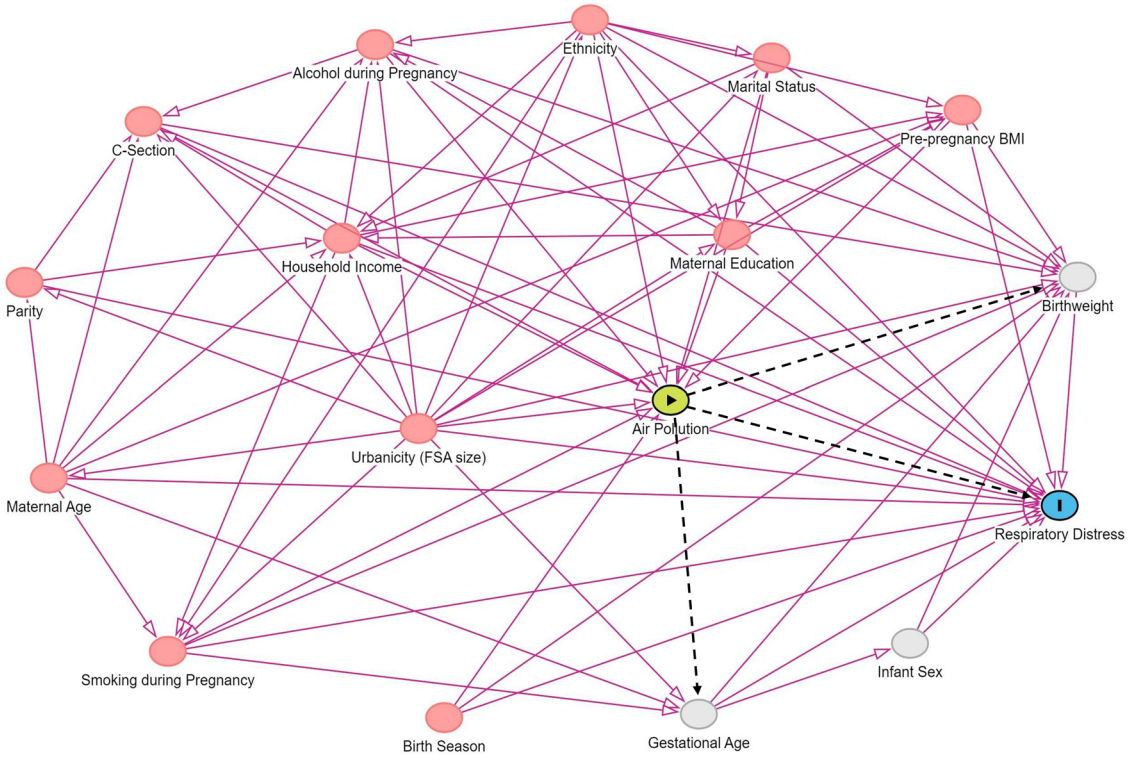

Figure 2. Figure 2 is a directed acyclic graph depicting the estimated direct effect of ambient air pollution exposure on neonatal respiratory distress. Parameters in red circles are potential confounding factors, and parameters in gray circles (birthweight, infant sex, and gestational age) are ancestors of the outcome only (i.e., cause of the outcome but not of the exposure). The air pollution exposure is represented by an arrow sign, and the neonatal respiratory distress outcome is denoted by a vertical line. The dotted lines between air pollution and respiratory distress and air pollution and gestational age indicate the causal path. According to the DAG, the minimal sufficient adjustment for estimating the total effect of ambient air pollution on neonatal respiratory distress is: alcohol during pregnancy, birth season, c-section, race/ethnicity, household income, marital status, maternal education, prepregnancy BMI, smoking during pregnancy, and urbanicity (FSA size). Note: BMI, body mass index; FSA, forward sortation area.

Table 1. Model covariates in the MIREC prospective cohort study, 2008–2011.

Outcomes	Infant sex	C-section	Maternal age	Parity	Overweight or obese	Alcohol	Smoking	Race/ethnicity	Income	Education	Marital status	Season	FSA size
$PM_{2.5}$ models													
Respiratory distress	—	x	—	x	x	—	—	x	x	x	x	—	x
Oxygen therapy	—	x	—	x	x	—	—	x	x	x	x	—	x
Assisted ventilation	—	x	x	x	—	—	—	x	x	x	x	—	x
Systemic antibiotics	—	x	—	x	—	—	—	x	x	x	x	—	x
NICU admission	—	x	x	x	x	x	x	x	x	x	x	—	x
Multiple interventions	—	x	—	x	x	—	—	x	x	x	x	—	x
Apgar 1min (low)	—	x	—	x	—	—	—	x	x	x	x	—	x
Apgar 1min (good)	—	x	—	x	—	—	—	x	x	x	x	—	x
NO_2 models													
Respiratory distress	x	x	—	x	x	—	—	x	x	x	x	x	x
Oxygen therapy	x	x	—	x	x	x	—	x	x	x	x	x	x
Assisted ventilation	x	x	x	x	x	—	—	x	x	x	x	x	x
Systemic antibiotics	x	x	—	x	x	—	—	x	x	x	x	x	x
NICU admission	x	x	x	x	x	—	x	x	x	x	x	x	x
Multiple interventions	x	x	—	x	x	—	—	x	x	x	x	x	x
Apgar 1 min (low)	x	x	—	x	x	—	—	x	x	x	x	x	x
Apgar 1 min (good)	x	x	—	x	x	—	x	x	x	x	x	x	x

Note: The table depicts covariates included in model 2 from Tables 6 and 7, for $PM_{2.5}$ and NO_2, respectively. Multiple interventions were defined as "yes" for neonates receiving two or more of the following interventions: oxygen therapy, assisted ventilation, and systemic antibiotics. Covariates included in each pollutant-outcome model are marked with an "x". These covariates were included in all sensitivity analyses and interaction models, unless otherwise noted. —, Not applicable; C-section, cesarean delivery; FSA, forward sortation area; MIREC, Maternal–Infant Research on Environmental Chemicals; NICU, neonatal intensive care unit; NO_2, nitrogen dioxide; $PM_{2.5}$, fine particulate matter.

reported moving to a different FSA during pregnancy. We conducted analyses excluding participants who moved to examine whether including participants who moved during pregnancy influenced our results. Finally, we conducted sensitivity analyses examining $PM_{2.5}$ and NO_2 among participants with complete data for both NO_2 and $PM_{2.5}$ data, adjusting for all model covariates included in either $PM_{2.5}$ and NO_2 models for each outcome.

In general, empirical standard error (SE) estimates have less statistical power but are more robust to model misspecification. Conversely, model-based SE estimates have more power but are more sensitive to model misspecification (personal communication with SAS technical support, Nov 2, 2021). Therefore, results based on empirical SE estimates were reported throughout the main paper. However, model-based SE results are reported in the Supplemental Material, Table S5. Models that failed to converge, generally due to a small number of outcomes or limited stratum-specific information, were not reported. Models for good or low Apgar score at 5 min and intermediary care unit admission, as well as fetal growth interaction models, were not reported for this reason. Statistical analyses were conducted in SAS (version 9.4; SAS Institute, Inc.). For descriptive statistics, missing values were excluded from the calculation of percentages, and average exposures were calculated based on arithmetic means. Hierarchical models were generated using the genmod procedure. Figures were generated using RStudio (version 2022.02.0). A threshold of $p < 0.05$ was considered statistically significant; values of $p > 0.05$ and ≤ 0.10 were considered marginally significant. All ORs in this paper are reported in relation to a 1-$\mu g/m^3$ increase in $PM_{2.5}$ or a 1-ppb increase in NO_2.

Results

Descriptive Statistics

Table 2 provides descriptive statistics for maternal and infant characteristics, as well as neonatal health outcomes, for participants in the $PM_{2.5}$ and NO_2 analyses. The majority of maternal participants were ≥30 years of age, White, highly educated, and had a household income of >Can$ 50,000. Few smoked during pregnancy (4%). Of the term infants in our analyses, 28% were born via C-section, <1% were LBW, and ∼6% were SGA. Approximately 67% of the neonates were full term (39–40 wk), vs. 28% early term (37–38 wk), and 15% late term (41–42 wk). Approximately 7% of the neonates experienced respiratory distress, 6% received oxygen therapy, 2% required assisted ventilation, and 3% received systemic antibiotics; 4% of neonates were admitted to the NICU. Respiratory distress presented early (<4 h after delivery) for most neonates who experienced it—that is, in 91% and 90% for those in the $PM_{2.5}$ and NO_2 analyses, respectively.

Table 3 shows exposure to $PM_{2.5}$ and NO_2 including prepregnancy, individual trimesters, and averages throughout pregnancy and prepregnancy. Median $PM_{2.5}$ and NO_2 levels during the study period were 8.81 $\mu g/m^3$ and 18.02 ppb, respectively. Trimester-specific $PM_{2.5}$ and NO_2 distributions were generally right skewed (Figures S1 and S2), and pollutant concentrations were highly correlated across exposure periods for both $PM_{2.5}$ ($r > 0.80$, Figure S3) and NO_2 ($r > 0.70$; Figure S4). Among participants with complete data for both pollutants ($n = 1{,}020$), $PM_{2.5}$ and NO_2 were modestly correlated ($r \sim 0.30$; Figure S5).

Table 4 provides descriptive statistics for health care interventions among neonates with and without respiratory distress among infants in the $PM_{2.5}$ and NO_2 analyses. Descriptive statistics for infants in the $PM_{2.5}$ analyses are summarized here; results for the NO_2 analyses were similar. Among neonates with respiratory distress, 79% received oxygen therapy, 23% received assisted ventilation, and 21% received systemic antibiotics; 34% of infants with respiratory distress were admitted to the NICU and 16% were admitted to an intermediate care unit. Almost one-third of neonates with respiratory distress received multiple interventions. As expected, only neonates with reported respiratory distress received oxygen therapy with or without assisted ventilation. Administration of systemic antibiotics and admission to the NICU or intermediate care units were not exclusive to those with respiratory distress. Only newborns experiencing respiratory distress received multiple interventions.

A more detailed breakdown of single and multiple interventions for neonates with and without respiratory distress in $PM_{2.5}$ analyses is provided in Table 5. Among neonates with respiratory distress, 8% received three interventions: oxygen therapy, assisted ventilation, and systemic antibiotics in either the NICU or an intermediate care unit. Another 17% received two interventions: either oxygen therapy and assisted ventilation (9%) in the

Table 2. Descriptive maternal and infant characteristics [*n* (%)] for participants included in $PM_{2.5}$ ($n = 1{,}321$) and NO_2 ($n = 1{,}064$) analyses in the MIREC prospective cohort study, 2008–2011.

Characteristics	$PM_{2.5}$ ($n = 1{,}321$)	NO_2 ($n = 1{,}064$)
Maternal		
Age (y)		
≤24	51 (3.9)	36 (3.4)
25–29	243 (18.4)	189 (17.8)
30–34	474 (35.9)	375 (35.2)
≥35	553 (41.9)	464 (43.6)
Ethnicity		
White	1,135 (85.9)	888 (83.5)
Non-White	186 (14.1)	176 (16.5)
Education (university degree)		
Yes	876 (66.3)	722 (67.9)
No	445 (33.7)	342 (32.1)
Household income		
≥Can$ 50,000	1,101 (83.4)	891 (83.7)
<Can$ 50,000	220 (16.6)	173 (16.3)
Married or long-term partner		
Yes	1,263 (95.6)	1,012 (95.1)
No	58 (4.4)	52 (4.9)
Parity (previous live births)		
≥1	719 (54.4)	604 (56.8)
0	602 (45.6)	460 (43.2)
Overweight or obese (prepregnancy)		
BMI ≥25	466 (35.3)	356 (33.5)
BMI <25	855 (64.7)	708 (66.5)
Smoked during pregnancy		
Yes	56 (4.2)	45 (4.2)
No	1,265 (95.8)	1,019 (95.8)
Consumed alcohol during pregnancy		
Yes	267 (20.2)	224 (21.0)
No	1,054 (79.8)	840 (79.0)
Urbanicity [FSA size (km^2)]		
<2	256 (19.4)	247 (23.2)
2–5	758 (57.4)	608 (57.1)
5–10	256 (19.4)	174 (16.4)
10–15	37 (2.8)	25 (2.4)
15–20	14 (1.1)	10 (0.9)
Moved during pregnancy		
Yes	104 (7.9)	88 (8.3)
No	1,217 (92.1)	976 (91.7)
Infant		
Sex		
Female	616 (46.6)	505 (47.5)
Male	705 (53.4)	559 (52.5)
Birth weight (g)		
<2,500	8 (0.6)	8 (0.8)
2,500–3,999	1,127 (85.3)	913 (85.8)
≥4,000	186 (14.1)	143 (13.4)
Low birth weight		
<2,500	8 (0.6)	8 (0.8)
≥2,500	1,313 (99.4)	1,056 (99.2)
Small for gestational age		
Yes	76 (5.8)	66 (6.2)
No	1,245 (94.2)	998 (93.8)
Gestational age at birth (wk)		
37	99 (7.5)	84 (7.9)
38	264 (20.0)	214 (20.1)
39	401 (30.4)	321 (30.2)
40	355 (26.9)	288 (27.1)
41	196 (14.8)	152 (14.3)
42	6 (0.5)	5 (0.5)
Mode of delivery		
C-section	371 (28.1)	292 (27.4)
Vaginal delivery	950 (71.9)	772 (72.6)
Birth season		
Warm: April–September	690 (52.2)	563 (52.9)
Cold: October–March	631 (47.8)	501 (47.1)
Neonatal health outcomes		
Physician-diagnosed respiratory distress		
Yes	96 (7.3)	87 (8.2)
No	1,225 (92.7)	977 (91.8)
Oxygen therapy		
Yes	76 (5.8)	65 (6.1)
No	1,245 (94.2)	999 (93.89)
Assisted ventilation		
Yes	22 (1.7)	22 (2.1)
No	1,299 (98.3)	1,042 (97.9)
Systemic antibiotics[a]		
Yes	34 (2.6)	32 (3.0)
No	1,284 (97.4)	1,029 (97.0)
Multiple interventions[b]		
Yes	25 (1.9)	24 (2.3)
No	1,296 (98.1)	1,040 (97.7)
NICU admission		
Yes	50 (3.8)	37 (3.5)
No	1,271 (96.2)	1,027 (96.5)
Intermediary care unit admission		
Yes	24 (1.8)	24 (2.3)
No	1,297 (98.2)	1,040 (97.7)
Apgar score at 1 min (low)[a]		
Yes	33 (2.5)	30 (2.8)
No	1,285 (97.5)	1,033 (97.2)
Apgar score at 1 min (good)[a]		
Yes	1,229 (93.2)	986 (92.8)
No	89 (6.8)	77 (7.2)
Apgar score at 5 min (low)[a]		
Yes	<5 (0.2)	<5 (0.2)
No	1,315 (99.8)	1,060 (99.8)
Apgar score at 5 min (good)[a]		
Yes	1,300 (98.7)	1,048 (98.7)
No	17 (1.3)	14 (1.3)

Note: BMI, body mass index; C-section, cesarean delivery; FSA, forward sortation area; MIREC, Maternal–Infant Research on Environmental Chemicals; NICU, neonatal intensive care unit; NO_2, nitrogen dioxide; $PM_{2.5}$, fine particulate matter.

[a]Missing values (<5 participants, representing 0.1%–0.3% of the total sample) were observed for both $PM_{2.5}$ and NO_2 analysis groups and were suppressed to protect participant confidentiality. Missing values were excluded from calculation of percentages in the table.

[b]Multiple interventions were defined as "yes" for neonates receiving two or more of the following interventions: oxygen therapy, assisted ventilation, and systemic antibiotics.

NICU or in an unspecified setting (e.g., in the labor and delivery room), or oxygen therapy and systemic antibiotics (8%) in the NICU or an intermediate care unit. None of the neonates received assisted ventilation and systemic antibiotics without oxygen therapy. The majority (62%) of neonates with respiratory distress received only one intervention: oxygen therapy (53%), assisted ventilation (5%), or systemic antibiotics (4%). Of the 96 neonates with respiratory distress, 6% were transferred to the NICU or intermediate care units without receiving any of the interventions described above. Finally, 5% of newborns with respiratory distress received none of the reported interventions and were not transferred to the NICU or intermediate care units, suggesting that the respiratory distress in those neonates was either self-limiting and of short duration or both.

Descriptive statistics for causes of respiratory distress, maternal health problems, and reasons for administering antibiotics (among neonates with and without respiratory distress) are provided in the Supplemental Material, Tables S1–S4. The cause of respiratory distress for most infants (74%) was unknown (Table S1). The prevalence of respiratory distress due to rare causes—that is, meconium aspiration syndrome (5%) and respiratory distress syndrome (3%), as well as fetal hydrops, pneumonia, and sepsis (1% each)—were consistent with their prevalence in the general population.[35] Among MIREC participants, 36% experienced metabolic disorders (diabetes, hypertension, or overweight/obesity) prior to pregnancy; 13% had gestational hypertension, preeclampsia, or gestational diabetes during pregnancy; and 4% were hospitalized more than once or for >1 d during pregnancy (Table S2). Antibiotics were primarily

Table 3. Descriptive statistics for exposures to $PM_{2.5}$ ($n = 1{,}321$) and NO_2 ($n = 1{,}064$) during prepregnancy and pregnancy in the MIREC prospective cohort study, 2008–2011.

Exposure periods	Min	5th P	25th P	50th P	Mean	75th P	95th P	Max
$PM_{2.5}$ [$\mu g/m^3$ ($n = 1{,}321$)]								
0	1.47	2.74	5.24	8.95	9.01	11.58	16.65	23.71
1	1.68	3.00	5.45	8.54	8.76	11.26	16.21	22.54
2	1.68	2.94	5.33	8.73	8.88	11.20	16.37	22.36
3	1.67	2.82	5.27	8.61	8.69	11.15	15.99	20.95
0–3	2.20	3.15	5.25	8.81	8.83	10.78	16.25	18.03
1–3	1.95	3.16	5.38	8.87	8.77	10.79	16.07	19.07
NO_2 [ppb ($n = 1{,}064$)]								
0	1.72	3.16	8.63	18.45	19.14	28.05	38.67	51.19
1	1.76	2.97	9.25	18.16	19.27	28.58	37.90	53.10
2	1.60	3.89	9.71	18.52	19.07	26.62	38.49	52.39
3	2.11	3.48	9.58	18.22	18.32	25.89	35.68	48.55
0–3	2.33	3.82	10.41	18.02	18.94	27.68	34.38	45.05
1–3	2.07	3.96	10.20	18.19	18.88	27.52	34.88	44.42

Note: Trimester 0 reflects the 3-month period prior to pregnancy. Trimesters 0–3 reflect average exposure across pregnancy, including prepregnancy. Trimesters 1–3 reflect average exposure across pregnancy, including trimesters 1–3. Max, maximum; min, minimum; MIREC, Maternal–Infant Research on Environmental Chemicals; NO_2, nitrogen dioxide; P, percentile; $PM_{2.5}$, fine particulate matter.

administered for prophylaxis for conditions such as suspected sepsis (35%) and maternal infections (29%) in MIREC neonates (Tables S3 and S4).

Air Pollution and Neonatal Outcomes

Tables 6 and 7 and Figures 3 and 4 show hierarchical logistic regression models analyses examining the associations between air pollution and neonatal health outcomes. Exposure to $PM_{2.5}$ was associated with a need for assisted ventilation, administration of systemic antibiotics, and multiple interventions in term neonates (Table 6, Figure 3). These associations were consistent across exposure periods—that is, during prepregnancy, individual trimesters, and total pregnancy (with and without the prepregnancy period)—as well as in models adjusted for detailed covariates.

Table 4. Descriptive statistics [*n* (%)] for health care interventions among neonates with ($n = 96$) and without ($n = 1{,}225$) respiratory distress in $PM_{2.5}$ analyses and among neonates with ($n = 87$) and without ($n = 977$) respiratory distress in nitrogen dioxide (NO_2) analyses ($n = 1{,}064$) in the MIREC prospective cohort study, 2008–2011.

	Neonates with respiratory distress	Neonates without respiratory distress
	Frequency (%)	Frequency (%)
$PM_{2.5}$ exposure	$n = 96$	$n = 1{,}225$
Oxygen therapy	76 (79.2)	0 (0)
Assisted ventilation	22 (22.9)	0 (0)
Systemic antibiotics	20 (21.1)[a]	14 (1.1)[a]
NICU admission	33 (34.4)	17 (1.4)
Intermediate care unit admission	15 (15.6)	9 (0.7)
Multiple interventions	25 (26.0)	0 (0)
NO_2 exposure	$n = 87$	$n = 977$
Oxygen therapy	65 (74.7)	0 (0)
Assisted ventilation	22 (25.3)	0 (0)
Systemic antibiotics	19 (22.1)[a]	13 (1.3)[a]
NICU admission	27 (31.0)	10 (1.0)
Intermediate care unit admission	16 (18.4)	8 (0.8)
Multiple interventions	24 (27.6)	0 (0)

Note: MIREC, Maternal–Infant Research on Environmental Chemicals; NICU, newborn intensive care unit; NO_2, nitrogen dioxide; $PM_{2.5}$, fine particulate matter.
[a]Missing values (<5) for systemic antibiotics were excluded from calculation of percentages.

$PM_{2.5}$ exposure was not significantly associated with respiratory distress at birth, oxygen therapy alone, NICU admission, or Apgar scores (good or low, at 1 min following delivery). For $PM_{2.5}$ analysis results, 95% confidence intervals and *p*-values based on empirical and model-based SE estimates were highly comparable (Table 6; Table S5).

Exposure to NO_2 was associated with administration of systemic antibiotics across exposure periods (Table 7 and Figure 4), and trimester-1 NO_2 exposure was marginally associated with multiple interventions. Finally, NO_2 exposure was inversely associated with a low 1-min Apgar score across several exposure periods. Associations between NO_2 exposure and neonatal outcomes were sensitive to covariate selection and SE calculation and were not consistent across exposure periods (Table 7; Table S5). NO_2 associations were not statistically significant when SEs were calculated using a model-based approach (Table S5).

Sensitivity Analyses

Given the differences in sample size and model covariates for $PM_{2.5}$ and NO_2 analyses, we conducted sensitivity analyses examining whether association between pollutant exposure and neonatal outcomes were consistent among participants with complete data for both $PM_{2.5}$ and NO_2 ($n = 1{,}020$) and adjusted for all potential covariates. Overall, associations between air pollution and adverse neonatal outcomes were similar to the results from the full $PM_{2.5}$ and NO_2 analyses (Table S6). $PM_{2.5}$ associations with multiple interventions and administration of antibiotics were comparable to results from the full data set, as were NO_2

Table 5. Descriptive statistics [*n* (%)] for single and multiple health care interventions among neonates with ($n = 96$) and without ($n = 1{,}225$) respiratory distress in $PM_{2.5}$ analyses in the MIREC prospective cohort study, 2008–2011.

Interventions	Neonates with respiratory distress ($n = 96$)	Neonates without respiratory distress ($n = 1{,}225$)
OT, AV, and SA (all settings)[a]	8 (8.3)	0 (0)
OT, AV, and SA (IntC + NICU)	<5 (2.1)[b]	—
OT, AV, and SA (NICU)	5 (5.2)	—
OT, AV, and SA (IntC)	<5 (1.0)[b]	—
OT and AV (all settings)[a]	9 (9.4)	0 (0)
OT and AV (NICU)	<5 (4.2)[b]	—
OT and AV	5 (5.2)	—
OT and SA (all settings)[a]	8 (8.3)	0 (0)
OT and SA (NICU)	7 (7.3)	—
OT and SA (IntC)	<5 (1.0)[b]	—
OT only (all settings)	51 (53.1)	0 (0)
OT only (NICU)	8 (8.3)	—
OT only (IntC)	7 (7.3)	—
OT only	36 (37.5)	—
AV only (all settings)	5 (5.2)	0 (0)
AV only (NICU)	<5 (2.1)[b]	—
AV only	<5 (3.1)[b]	—
SA only (all settings)	<5 (4.2)[b]	14 (1.1)
SA only (NICU)	<5 (2.1)[b]	5 (0.4)
SA only (IntC)	<5 (1.0)[b]	<5 (0.2)[b]
SA only	<5 (1.0)[b]	7 (0.6)
No intervention (all settings)	11 (11.5)	1,211 (98.9)
IntC, NICU	0 (0)	<5 (0.1)[b]
NICU	<5 (3.1)[b]	11 (0.9)
IntC	<5 (3.1)[b]	6 (0.5)
Other	5 (5.2)	1,193 (97.4)

Note: —, not applicable; AV, assisted ventilation; IntC, intermediate care unit admission; MIREC, Maternal–Infant Research on Environmental Chemicals; NICU, neonatal intensive care unit admission; OT, oxygen therapy; $PM_{2.5}$, fine particulate matter; SA, systemic antibiotics.
[a]Neonates with multiple interventions.
[b]Cell counts with <5 participants suppressed to protect confidentiality.

Table 6. $PM_{2.5}$ and neonatal health outcomes in the MIREC prospective cohort study, 2008–2011 ($n = 1{,}321$).

	Model 1[a,b]			Model 2[a,c,d]		
Exposure periods	OR	95% CI[e]	*p*-Value	OR	95% CI[e]	*p*-Value
Respiratory distress ($n = 1{,}321$)						
0	0.98	(0.92, 1.04)	0.4819	0.98	(0.93, 1.04)	0.5350
1	0.99	(0.93, 1.07)	0.8860	1.00	(0.94, 1.07)	0.9954
2	0.97	(0.91, 1.04)	0.4518	0.98	(0.92, 1.04)	0.5094
3	0.99	(0.93, 1.05)	0.6556	0.99	(0.93, 1.05)	0.7501
0–3	0.98	(0.92, 1.05)	0.5875	0.99	(0.92, 1.05)	0.6707
1–3	0.98	(0.92, 1.05)	0.6352	0.99	(0.92, 1.06)	0.7275
Oxygen therapy ($n = 1{,}321$)						
0	0.99	(0.90, 1.08)	0.7574	0.99	(0.91, 1.09)	0.8659
1	0.98	(0.90, 1.08)	0.7174	0.99	(0.91, 1.08)	0.8374
2	0.97	(0.90, 1.05)	0.4662	0.98	(0.91, 1.05)	0.5580
3	0.97	(0.90, 1.06)	0.5265	0.98	(0.90, 1.06)	0.6254
0–3	0.98	(0.89, 1.07)	0.6050	0.98	(0.90, 1.08)	0.7143
1–3	0.97	(0.89, 1.06)	0.5512	0.98	(0.90, 1.07)	0.6581
Assisted ventilation ($n = 1{,}321$)						
0	1.12	(1.02, 1.23)	0.0148	1.13	(1.02, 1.24)	0.0178
1	1.15	(1.04, 1.27)	0.0066	1.16	(1.04, 1.29)	0.0097
2	1.11	(0.98, 1.25)	0.1079	1.11	(0.98, 1.27)	0.1010
3	1.16	(1.04, 1.30)	0.0097	1.17	(1.04, 1.32)	0.0106
0–3	1.16	(1.02, 1.32)	0.0244	1.17	(1.02, 1.35)	0.0291
1–3	1.16	(1.02, 1.33)	0.0227	1.18	(1.02, 1.36)	0.0266
Systemic antibiotics ($n = 1{,}318$)						
0	1.10	(1.03, 1.18)	0.0077	1.10	(1.03, 1.18)	0.0064
1	1.11	(1.04, 1.18)	0.0015	1.11	(1.04, 1.18)	0.0008
2	1.10	(1.00, 1.21)	0.0485	1.10	(1.00, 1.21)	0.0409
3	1.10	(1.04, 1.16)	0.0005	1.10	(1.04, 1.16)	0.0006
0–3	1.12	(1.03, 1.21)	0.0062	1.12	(1.04, 1.21)	0.0043
1–3	1.12	(1.03, 1.21)	0.0049	1.12	(1.04, 1.21)	0.0031
NICU admission ($n = 1{,}321$)						
0	0.97	(0.90, 1.05)	0.4771	0.97	(0.90, 1.05)	0.4992
1	0.98	(0.90, 1.08)	0.7041	0.98	(0.90, 1.08)	0.7354
2	0.99	(0.89, 1.09)	0.7716	0.99	(0.89, 1.09)	0.8000
3	0.97	(0.91, 1.03)	0.3461	0.97	(0.91, 1.04)	0.3726
0–3	0.97	(0.89, 1.07)	0.5695	0.98	(0.89, 1.07)	0.5972
1–3	0.98	(0.89, 1.07)	0.6123	0.98	(0.89, 1.07)	0.6419
Multiple interventions ($n = 1{,}321$)						
0	1.12	(1.04, 1.21)	0.0018	1.13	(1.05, 1.21)	0.0013
1	1.14	(1.08, 1.21)	0.0000	1.15	(1.07, 1.23)	0.0001
2	1.11	(1.02, 1.20)	0.0157	1.11	(1.03, 1.20)	0.0105
3	1.14	(1.08, 1.19)	<0.000001	1.15	(1.09, 1.21)	<0.0001
0–3	1.15	(1.07, 1.24)	0.0002	1.16	(1.07, 1.26)	0.0003
1–3	1.15	(1.08, 1.22)	0.0000	1.16	(1.08, 1.24)	<0.0001
Apgar 1 min [low ($n = 1{,}318$)]						
0	1.00	(0.95, 1.06)	0.9179	1.01	(0.95, 1.07)	0.7738
1	1.01	(0.94, 1.08)	0.8361	1.01	(0.94, 1.10)	0.7141
2	1.00	(0.93, 1.07)	0.9589	1.00	(0.93, 1.08)	0.9231
3	0.99	(0.92, 1.07)	0.8251	1.00	(0.92, 1.08)	0.9483
0–3	1.00	(0.93, 1.08)	0.9960	1.01	(0.93, 1.09)	0.8630
1–3	1.00	(0.93, 1.08)	0.9780	1.01	(0.93, 1.09)	0.8944
Apgar 1 min [good ($n = 1{,}318$)]						
0	1.04	(0.98, 1.10)	0.1633	1.04	(0.98, 1.09)	0.2155
1	1.01	(0.97, 1.06)	0.6126	1.00	(0.96, 1.05)	0.8419
2	1.04	(1.00, 1.09)	0.0792	1.04	(0.99, 1.08)	0.1196
3	1.03	(0.99, 1.07)	0.1703	1.02	(0.98, 1.06)	0.2711
0–3	1.04	(0.99, 1.09)	0.1688	1.03	(0.98, 1.08)	0.2471
1–3	1.03	(0.99, 1.08)	0.1895	1.02	(0.98, 1.07)	0.2927

Note: Hierarchical, multiple logistic regression model results. C-section, cesarean delivery; CI, confidence interval; FSA, forward sortation area; MIREC, Maternal–Infant Research on Environmental Chemicals; NICU, neonatal intensive care unit admission; OR, odds ratio; $PM_{2.5}$, fine particulate matter.

[a]Model 1 adjusts for covariates associated with $PM_{2.5}$ exposure and the outcome of interest. Model 2 adjusts for covariates in model 1 plus FSA size, a surrogate for urbanicity. All models adjust for center as a random effect.

[b]Model 1 included the following covariates as fixed effects for each outcome: respiratory distress: C-section, parity, overweight or obese, ethnicity, income, education, and marital status; oxygen therapy: C-section, parity, overweight or obese, ethnicity, income, education, and marital status; assisted ventilation: C-section, maternal age, parity, ethnicity, income, education, and marital status; systemic antibiotics: C-section, parity, ethnicity, income, education, and marital status; NICU admission: C-section, maternal age, parity, overweight or obese, alcohol, smoking, ethnicity, income, education, and marital status; multiple interventions: C-section, parity, overweight or obese, ethnicity, income, education, and marital status; Apgar 1 min (low): C-section, parity, ethnicity, income, education, and marital status; Apgar 1 min (good): C-section, parity, ethnicity, income, education, and marital status.

[c]Model 2 included FSA size as a surrogate for urbanicity, in addition to model 1 covariates.

[d]Model 2 results are graphically depicted in Figure 3.

[e]ORs are reported for each 1-$\mu g/m^3$ increase in $PM_{2.5}$.

Table 7. NO_2 and neonatal health outcomes in the MIREC prospective cohort study, 2008–2011 ($n = 1{,}064$).

	Model 1[a,b]			Model 2[a,c,d]		
Exposure periods	OR	95% CI[e]	*p*-Value	OR	95% CI[e]	*p*-Value
Respiratory distress ($n = 1{,}064$)						
0	0.99	(0.95, 1.02)	0.4938	0.99	(0.95, 1.03)	0.5169
1	0.99	(0.96, 1.02)	0.3988	0.99	(0.96, 1.02)	0.4283
2	1.00	(0.97, 1.03)	0.9867	1.00	(0.97, 1.03)	0.9437
3	1.00	(0.96, 1.04)	0.9529	1.00	(0.96, 1.04)	0.9858
0–3	0.99	(0.96, 1.03)	0.6731	0.99	(0.96, 1.03)	0.7014
1–3	0.99	(0.96, 1.03)	0.7587	1.00	(0.96, 1.03)	0.7903
Oxygen therapy ($n = 1{,}064$)						
0	0.99	(0.96, 1.03)	0.7082	1.00	(0.96, 1.03)	0.8146
1	0.99	(0.96, 1.02)	0.5946	0.99	(0.96, 1.02)	0.6997
2	1.00	(0.96, 1.03)	0.8541	1.00	(0.96, 1.04)	0.9840
3	0.99	(0.95, 1.04)	0.7056	0.99	(0.95, 1.04)	0.8026
0–3	0.99	(0.95, 1.03)	0.7066	1.00	(0.96, 1.04)	0.8163
1–3	0.99	(0.95, 1.03)	0.7086	1.00	(0.96, 1.04)	0.8198
Assisted ventilation ($n = 1{,}064$)						
0	1.03	(0.99, 1.06)	0.1316	1.03	(0.99, 1.07)	0.1240
1	1.02	(0.99, 1.05)	0.2722	1.02	(0.98, 1.06)	0.2756
2	1.02	(0.97, 1.07)	0.4921	1.02	(0.97, 1.08)	0.4519
3	1.03	(0.97, 1.09)	0.3374	1.03	(0.97, 1.10)	0.3002
0–3	1.03	(0.98, 1.08)	0.2709	1.03	(0.98, 1.09)	0.2457
1–3	1.03	(0.98, 1.08)	0.3207	1.03	(0.98, 1.09)	0.2911
Systemic antibiotics ($n = 1{,}061$)						
0	1.02	(1.00, 1.04)	0.0384	1.02	(1.00, 1.04)	0.0168
1	1.03	(1.01, 1.05)	0.0064	1.03	(1.01, 1.05)	0.0025
2	1.03	(1.00, 1.07)	0.0734	1.04	(1.00, 1.07)	0.0509
3	1.02	(0.99, 1.06)	0.2049	1.02	(0.99, 1.06)	0.1624
0–3	1.03	(1.00, 1.06)	0.0455	1.03	(1.00, 1.06)	0.0217
1–3	1.03	(1.00, 1.07)	0.0531	1.03	(1.00, 1.07)	0.0286
NICU admission ($n = 1{,}064$)						
0	0.99	(0.97, 1.02)	0.6325	1.00	(0.97, 1.02)	0.7172
1	1.00	(0.98, 1.02)	0.9739	1.00	(0.98, 1.02)	0.8358
2	1.01	(0.98, 1.04)	0.6840	1.01	(0.98, 1.04)	0.5509
3	1.00	(0.97, 1.03)	0.9635	1.00	(0.97, 1.03)	0.9236
0–3	1.00	(0.97, 1.03)	0.9827	1.00	(0.98, 1.03)	0.8854
1–3	1.00	(0.97, 1.03)	0.8948	1.00	(0.98, 1.03)	0.7561
Multiple interventions ($n = 1{,}064$)						
0	1.01	(1.00, 1.03)	0.1623	1.01	(1.00, 1.03)	0.1316
1	1.01	(1.00, 1.02)	0.0151	1.02	(1.00, 1.03)	0.0567
2	1.00	(0.97, 1.02)	0.8668	1.00	(0.97, 1.03)	0.9801
3	1.00	(0.97, 1.02)	0.7900	1.00	(0.97, 1.03)	0.9330
0–3	1.01	(0.99, 1.03)	0.5455	1.01	(0.99, 1.03)	0.4595
1–3	1.00	(0.98, 1.02)	0.7109	1.01	(0.98, 1.03)	0.5978
Apgar 1 min: low ($n = 1{,}063$)						
0	0.97	(0.95, 1.00)	0.0377	0.97	(0.94, 1.01)	0.1181
1	0.97	(0.94, 1.00)	0.0796	0.97	(0.93, 1.01)	0.1546
2	0.95	(0.92, 0.99)	0.0058	0.95	(0.91, 0.99)	0.0224
3	0.95	(0.93, 0.98)	0.0003	0.95	(0.92, 0.98)	0.0038
0–3	0.96	(0.93, 0.99)	0.0090	0.96	(0.92, 1.00)	0.0384
1–3	0.95	(0.92, 0.99)	0.0060	0.96	(0.92, 0.99)	0.0266
Apgar 1 min: good ($n = 1{,}063$)						
0	1.03	(1.01, 1.05)	0.0037	1.03	(1.00, 1.05)	0.0243
1	1.03	(1.01, 1.05)	0.0162	1.03	(1.00, 1.05)	0.0574
2	1.03	(1.00, 1.05)	0.0565	1.02	(0.99, 1.05)	0.1353
3	1.03	(1.01, 1.05)	0.0066	1.03	(1.00, 1.05)	0.0376
0–3	1.03	(1.01, 1.06)	0.0059	1.03	(1.00, 1.06)	0.0348
1–3	1.03	(1.01, 1.06)	0.0106	1.03	(1.00, 1.06)	0.0495

Note: Hierarchical, multiple logistic regression model results. C-section, cesarean delivery; CI, confidence interval; FSA, forward sortation area; MIREC, Maternal–Infant Research on Environmental Chemicals; NICU, neonatal intensive care unit admission; NO_2, nitrogen dioxide; OR, odds ratio.

[a]Model 1 adjusts for covariates associated with NO_2 exposure and the outcome of interest. Model 2 adjusts for covariates in model 1 plus FSA size, a surrogate for urbanicity. All models adjust for center as a random effect.

[b]Model 1 included the following covariates as fixed effects for each outcome: respiratory distress: infant sex, C-section, parity, overweight or obese, ethnicity, income, education, marital status, and season; oxygen therapy: infant sex, C-section, parity, overweight or obese, alcohol, ethnicity, income, education, marital status, and season; assisted ventilation: infant sex, C-section, maternal age, parity, overweight or obese, ethnicity, income, education, marital status, and season; systemic antibiotics: infant sex, C-section, parity, overweight or obese, ethnicity, income, education, marital status, and season; NICU admission: infant sex, C-section, maternal age, parity, overweight or obese, smoking, ethnicity, income, education, marital status, and season; multiple interventions: infant sex, C-section, parity, overweight or obese, ethnicity, income, education, marital status, and season; Apgar 1 min (low): infant sex, C-section, parity, overweight or obese, ethnicity, income, education, marital status, and season; Apgar 1 min (good): infant sex, C-section, parity, overweight or obese, smoking, ethnicity, income, education, marital status, and season.

[c]Model 2 included FSA size as a surrogate for urbanicity, in addition to model 1 covariates.

[d]Model 2 results are graphically depicted in Figure 4.

[e]ORs are reported for each 1-ppb increase in NO_2.

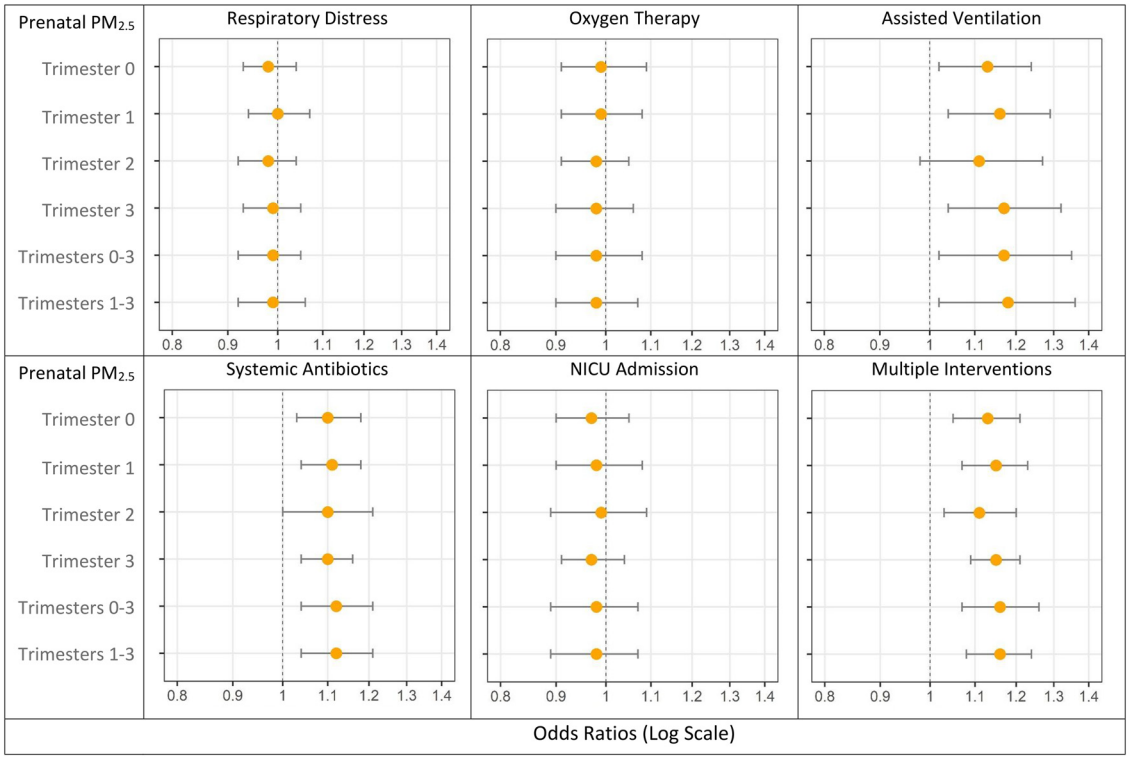

Figure 3. Prenatal exposure to fine particulate matter ($PM_{2.5}$) and adverse neonatal health outcomes in the MIREC prospective cohort study, 2008–2011, ($n = 1{,}321$). Numeric data of adjusted odds ratios (ORs) and 95% confidence intervals (CIs) obtained from model 2 are described in Table 6. Error bars represent the 95% CIs. Multiple interventions were defined as "yes" for neonates receiving two or more of the following interventions: administration of oxygen therapy, assisted ventilation, and systemic antibiotics. Results are presented on a logarithmic scale. ORs are reported for each increase in 1-$\mu g/m^3$ increase in $PM_{2.5}$. Note: MIREC, Maternal–Infant Research on Environmental Chemicals; NICU, neonatal intensive care unit.

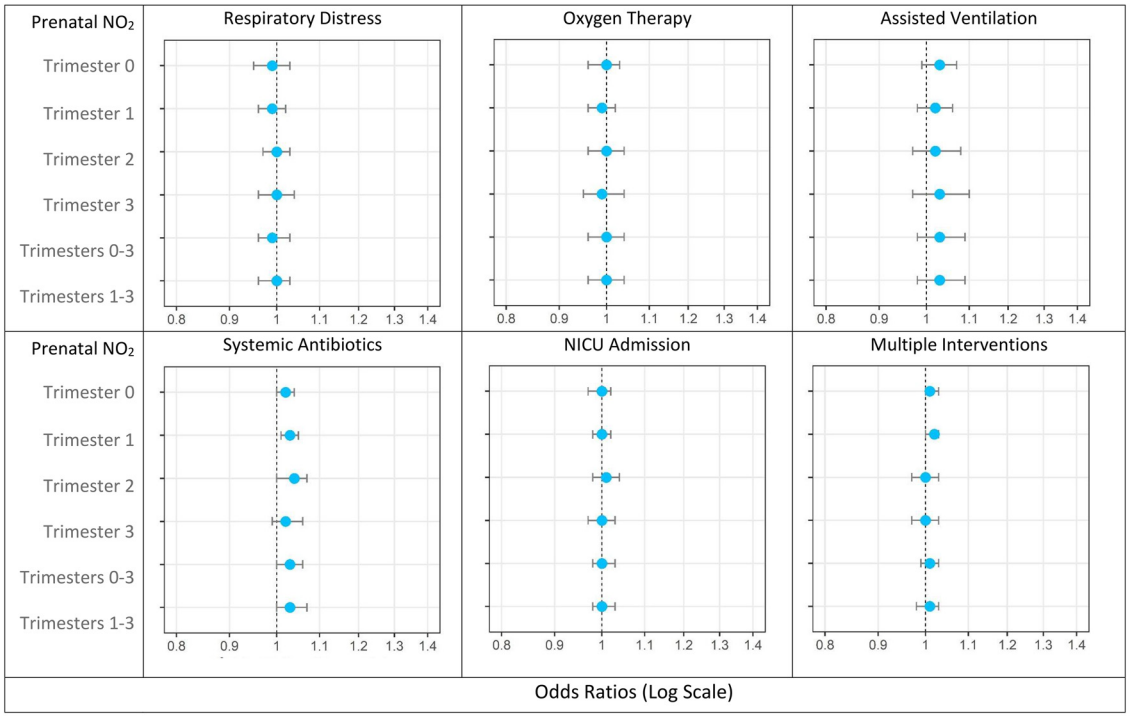

Figure 4. Prenatal exposure to nitrogen dioxide (NO_2) and adverse neonatal health outcomes in the Maternal-Infant Research on Environmental Chemicals prospective cohort study, 2008–2011 ($n = 1{,}064$). Numeric data of adjusted odds ratios (ORs) and 95% confidence intervals (CIs) obtained from Model 2 are described in Table 7. Error bars represent 95% CIs. Multiple interventions were defined as "yes" for neonatesreceiving two or more of the following interventions: oxygen therapy, assisted ventilation, and systemic antibiotics. Results are presented on a logarithmic scale. ORs are reported for each 1-ppb increase in NO_2. Note: NICU, neonatal intensive care unit.

associations with antibiotics. Associations between $PM_{2.5}$ and assisted ventilation were weaker, as were associations between NO_2 and Apgar scores.

Participants missing >25% of daily air pollution estimates, due to gaps in the NAPS data, were excluded from the analyses. Adjusted model results were similar (OR ≤10% different) when participants with missing data were included (Table S7). However, associations between NO_2 exposure and neonatal outcomes were slightly stronger in models with any measurements vs. models limited to participants with ≥75%. Associations between air pollution and adverse neonatal outcomes were also similar when participants who moved were excluded from the analyses (Table S8).

We further conducted sensitivity analyses to assess the impact of NICU admission and respiratory distress classifications. Associations between air pollution and NICU admissions were similar (OR ≤10% different) for NICU admissions with and without respiratory distress, with slightly more positive associations between $PM_{2.5}$ and NICU admission with respiratory distress vs. NICU admission without respiratory distress (Table S9). Finally, associations between air pollution and neonatal outcomes were similar when we restricted our analyses to neonates in whom respiratory distress was reported within 4 h of delivery (Table S10).

Interactions and Effect Modification

There was some evidence that fetal growth indicators such as LBW and SGA were associated with the neonatal outcomes in our analyses. Descriptive statistics for neonatal health outcomes by BW category (low, normal, and high) and SGA category are provided in Tables S11 and S12. In ANOVA analyses, assisted ventilation (among neonates in the $PM_{2.5}$ analyses only) and NICU admission varied significantly by BW category (Table S12), whereas respiratory distress and NICU admission varied significantly between SGA and non-SGA neonates (Table S12).

We hypothesized that fetal growth could act as an effect modifier in our analyses. However, we lacked sufficient statistical power to examine potential interactions. Therefore, we conducted sensitivity analyses excluding LBW and SGA neonates from the analyses. Associations between air pollution and adverse neonatal outcomes were similar in models excluding LBW neonates only, as well as in models excluding both LBW and SGA neonates (Tables S13 and S14).

We also considered gestational age as a potential effect modifier. Descriptive statistics and ANOVA results for gestational age (GA; early term, full term, and later term) are provided in Table S15. Most health outcomes did not vary significantly between neonates who were early term (37–38 wk), full term (39–40 wk), and late term (41–42 wk) at delivery. The prevalence of good Apgar scores at 1 min varied significantly by GA, with a slightly lower prevalence of good Apgar scores in late-term infants.

Partially stratified interaction models for GA category (early, full, and late term) and air pollution exposures are provided in Tables S16 and S17. Associations between $PM_{2.5}$ and adverse neonatal outcomes were generally stronger in early-term neonates. Most associations were similar in direction for early-, full-, and late-term infants, merely differing in effect magnitude and precision. However, there was some evidence to suggest that $PM_{2.5}$ was inversely associated with respiratory distress in late-term neonates. These associations should be interpreted with caution owing to the small stratum size. Associations between air pollution and systemic antibiotics appeared to be stronger for early- and late-term neonates compared with full-term infants for both $PM_{2.5}$ and NO_2.

Finally, we examined the impact of maternal health problems during and prior to pregnancy on associations between air pollution and neonatal health outcomes. Multiple or extended hospitalizations during pregnancy were the strongest effect modifiers, exhibiting significant interactions with $PM_{2.5}$ in hierarchical multiple logistic regression models for respiratory distress, oxygen therapy, assisted ventilation, and Apgar scores (Table S18). Interestingly, metabolic disorders during pregnancy (gestational hypertension, preeclampsia, impaired glucose tolerance, or gestational diabetes) were not strong effect modifiers (Table S18). However, metabolic disorders (diabetes, hypertension, and overweight/obesity) prior to pregnancy were stronger effect modifiers compared with other prepregnancy health problems, namely, maternal asthma, any health problems, and diabetes or hypertension alone (Table S19). Furthermore, the impact of maternal hospitalizations during pregnancy and metabolic disorders prior to pregnancy remained significant when included in the same models (Table S20). $PM_{2.5}$ interactions with maternal hospitalizations and metabolic disorders prior to pregnancy were positive, suggesting that associations between $PM_{2.5}$ exposure and adverse neonatal health outcomes were stronger among participants with preexisting metabolic disorders or pregnancy hospitalizations. In contrast, we observed inverse interactions with $PM_{2.5}$ exposure for several maternal health indicators, including complications, acute health problems, and metabolic disorders during pregnancy (Table S21). For NO_2, we observed both negative and inconsistent interactions between maternal health problems and exposure (Tables S22–S24).

Discussion

We examined associations between prenatal exposures to ambient air pollutants and respiratory distress in term neonates using data from a multicity, prospective pregnancy cohort. Prenatal $PM_{2.5}$ exposures were strongly associated with severe respiratory distress as indicated by the need of assisted ventilation and multiple clinical interventions, as well as by administration of systemic antibiotics. These associations were consistent across different exposure periods (i.e., individual trimesters, prepregnancy, and total pregnancy averages) and were robust to alternative model specifications. Prenatal NO_2 exposures were also associated with administration of systemic antibiotics. These results provide insights that can be used to address a significant, modifiable risk factor for a globally relevant adverse neonatal health outcome.

Respiratory distress in neonates is a broad term used to describe one or more symptoms of breathing difficulty (e.g., tachypnea, nasal flaring, chest retractions, grunting) caused by heterogeneous syndromes and illnesses. Moreover, the presentation, severity, and treatment of respiratory distress vary based on the underlying etiology.[36] Our results suggest that maternal $PM_{2.5}$ exposures were associated with severe respiratory distress in term neonates that required assisted ventilation, systemic antibiotic use, or multiple interventions. Notably, all cases requiring multiple interventions in our study population reported oxygen therapy along with some combination of assisted ventilation and systemic antibiotic use, which suggests that oxygen therapy alone may not be a good indicator of severe respiratory distress. The associations between $PM_{2.5}$ (and to a lesser degree, NO_2) exposure with systemic antibiotic use may suggest a potential mechanism for air pollution-induced respiratory distress through increased susceptibility to bacterial infections.

The association between prenatal air pollution exposure and severe respiratory distress in neonates is unique but not surprising. Exposure to air pollution, even at the lower levels observed in Canada, has been linked with adverse respiratory outcomes in children and adults[32,52–59] and with adverse neonatal outcomes.[10,42,46–48,53,60] But despite the global burden and impact of neonatal respiratory distress, only one previous study[40]—to our knowledge—has examined the potential impact of air pollution on this outcome. Based on a large administrative cohort in the United

States, Seeni et al. reported associations between exposure to $PM_{2.5}$ during pregnancy and transient tachypnea of newborn, whereas nitrogen oxides (NOx) exposures were associated with respiratory distress syndrome.[40] Associations were similar for preterm, early-term (≤37 wk) infants, with slightly stronger associations for NOx in term infants and in early and term infants for $PM_{2.5}$.

In contrast with Seeni et al.,[40] we observed no associations between air pollution exposures and general respiratory distress. However, we observed strong associations between $PM_{2.5}$ exposure and indicators of severe respiratory distress, including multiple interventions and assisted ventilation. We also found that $PM_{2.5}$ exposure was a stronger predictor of respiratory distress outcomes compared with NO_2 exposure, whereas Seeni et al.[40] reported more consistent associations between NOx and respiratory distress. Differences in our neonatal populations, including GA at birth—as well as the methodologies we used to estimate air pollution and define respiratory distress—may have contributed to the observed discrepancies in our results.

We limited our analyses to term births, whereas Seeni et al.[40] included both term and preterm births, conducting stratified analyses to consider early preterm (23–34 wk), near-term (35–38 wk), and term (38–42 wk) neonates. The small number of premature deliveries in the MIREC Study ($n = 38$ and $n = 31$ for $PM_{2.5}$ and NO_2 analyses, respectively, after other exclusions were applied) limited our ability to draw any meaningful conclusions between $PM_{2.5}$ exposure and respiratory distress in premature neonates. However, we did observe stronger associations between air pollution exposure and respiratory distress severity indicators among early-term neonates (37–38 wk) compared with full- and late-term infants. This is significant because the causes and pathogeneses of neonatal respiratory distress vary based on the GA.[36] For example, the most common cause of respiratory distress in premature newborns is neonatal respiratory distress syndrome, characterized by surfactant deficiency,[61] whereas transient tachypnea is the most common cause of respiratory distress in term neonates.[36,61] Moreover, other less common causes, such as meconium aspiration syndrome, are more prevalent in term neonates compared with preterm neonates.[36] Future studies with a larger number of premature neonates are needed to explore the complex interactions between prenatal air pollution exposure, prematurity, and respiratory distress in this population.

The retrospective cohort study by Seeni et al. used ICD-9 codes alone to identify children with respiratory conditions from an administrative database.[40] Although the use of administrative data provided a much larger sample size ($N = 223{,}375$) for investigating associations between air pollution and respiratory distress, there are some disadvantages. ICD codes are less accurate than medical record review for identifying disease outcomes,[62–64] particularly for diseases with poor case definition and lacking specific symptoms.[62] Previous studies have reported difficulty identifying respiratory distress based on ICD codes in administrative data[65] owing to low sensitivity and specificity of ICD codes for neonatal respiratory conditions.[66]

We conducted our analyses using clinical outcomes based on medical record review—including physician-diagnosed respiratory distress—in a prospective, multisite pregnancy cohort. This approach minimized misclassification of respiratory distress outcomes and allowed us to examine respiratory distress severity and interventions, as well as NICU admissions and Apgar scores. We found stronger associations between air pollution and respiratory distress severity compared with respiratory distress alone, suggesting that ancillary clinical data were important in identifying impacts of air pollution on neonatal outcomes.

Seeni et al.[40] used the Community Multiscale Air Quality Model to estimate a suite of pollutants, including $PM_{2.5}$ and NOx. We estimated $PM_{2.5}$ and NO_2 levels based on satellite and land-use regression models combined with surveillance monitoring data. This approach allowed us to examine different exposure periods during pregnancy at a finer spatial scale. However, reduced sample size due to missing NO_2 monitoring data limited our ability to estimate associations between NO_2 exposures and neonatal outcomes, as well as to compare $PM_{2.5}$ and NO_2 results. Finally, Seeni et al.[40] examined associations using multipollutant models, whereas we examined single-pollutant models.

Our findings demonstrate, importantly, that maternal air pollution exposures during pregnancy may be associated with more severe respiratory distress in term neonates. These results add to the existing research linking air pollution exposure with adverse maternal and neonatal outcomes. Although underlying biological mechanisms that may be driving these associations have not been fully characterized in humans, several possible mechanisms have been identified.

A number of physiological mechanisms may explain the adverse effects of prenatal air pollution exposure on fetal growth and lung development. The most well characterized include increased inflammation, oxidative stress, and placental disruption,[21,26,67,68] with growing evidence that air pollution exposures impact genetic and epigenetic factors that mediate lung and immune system development.[21,26] Animal studies have shown that *in utero* $PM_{2.5}$ exposures can significantly disturb distal lung epithelium and mesenchyme differentiation during the saccular stage of lung development and suppress the expression of lung development-related genes,[69] as well as alter host immune responses and increase oxidative stress and risk of respiratory infections.[70] Finally, the reduced capacity for repair in developing lung tissues may cause heightened susceptibility to respiratory stressors.[26] $PM_{2.5}$ and NO_2 exposures may have increased susceptibility to, and severity of, lung disease in MIREC neonates by enhancing pro-inflammatory systemic and pulmonary responses, a mechanistic pathway consistent with our observed associations between air pollution and systemic antibiotic use, as well as with previous studies that have linked prenatal air pollution exposure with elevated pro-inflammatory markers in the MIREC cohort.[10,45]

In addition to linkages with respiratory distress, we observed counterintuitive associations between NO_2 exposure and low Apgar score at 1 min. These associations were weaker in models adjusting for urbanicity, suggesting that they may be partially due to residual confounding. The associations may also be explained by limitations in the Apgar score. Although widely used as an indicator of neonatal health, Apgar scores are subjective, nonspecific indicators of gross clinical abnormalities.[49] Apgar scores provide a useful indicator of neonatal condition at a single time point but can be affected by a number of maternal and fetal factors, as well as by interobserver variability.[49] Importantly, Apgar scores are not comparable between infants who have received resuscitation interventions and those who have not.[49] Finally, Apgar score was not a good predictor of neonatal respiratory distress in our study population; that is, more than half of the neonates with respiratory distress had a good Apgar score at 1 min, and 28% of neonates who received multiple interventions had a good Apgar score at 1 min, whereas Apgar score at 5 min did not provide sufficient variability to identify at-risk neonates in the MIREC Study.

Multiple epidemiological studies have shown that *in utero* $PM_{2.5}$ and NO_2 exposures are associated with LBW and SGA. LBW and SGA are independent risk factors for respiratory distress[23,24,71]; therefore, we considered LBW and SGA status in our analyses. Adverse neonatal outcomes varied significantly by fetal growth measures in our study population. However, associations between air pollution exposure and adverse neonatal respiratory outcomes were similar in models with or without LBW and SGA neonates, suggesting that air pollution is likely a

modifiable factor for neonatal respiratory outcomes independent of fetal growth measures. Future analyses in cohorts with a higher prevalence of LBW and SGA neonates are needed to understand potential effect modification or mediation of air pollution impacts by fetal growth.

Maternal health status was a significant modifier of associations between air pollution and neonatal outcomes in MIREC neonates. Multiple or extended maternal hospitalizations during pregnancy was the strongest effect modifier, displaying significant positive interactions with $PM_{2.5}$ exposures for respiratory distress, oxygen therapy, assisted ventilation, and Apgar scores. A history of metabolic disorders prior to pregnancy (diabetes, hypertension, or overweight/obesity) was also a strong positive effect modifier of $PM_{2.5}$ associations with oxygen therapy, systemic antibiotics, and multiple interventions. Previous studies have identified maternal morbidities and pregnancy complications as important effect modifiers for air pollution-mediated birth outcomes, such as preterm labor.[72,73] The increased risks of metabolic disorders[74,75] and hospitalization[74,76] associated with air pollution are well documented. Previous studies have also reported associations between air pollution and pregnancy complications,[77] suggesting that maternal morbidity may act as a mediator for air pollution-induced neonatal outcomes. This would be consistent with results of a previous study that identified diabetes as a mediator for air pollution-induced atherosclerotic plaque burden.[78] To our knowledge, this is the first study to identify maternal health problems as effect modifiers for neonatal respiratory distress outcomes. In contrast, maternal health problems and complications that developed during pregnancy were not positive effect modifiers and, in some cases, even displayed significant inverse interactions with air pollution. This may be due to increased oversight and/or preemptive care for these pregnancies, potentially mitigating the adverse effects of air pollution on neonatal respiratory distress outcomes.

We found no evidence to suggest that associations between air pollution exposure and respiratory distress outcomes varied by timing of exposure. Previous studies identified critical windows for air pollution susceptibility during pregnancy with respect to adverse birth outcomes[42,79,80] and childhood asthma.[30] However, these studies focused on different outcomes. Furthermore, our analyses focused on trimesters, which may not be the best approach for identifying critical windows of air pollution susceptibility because trimester-level exposures are highly correlated and because critical windows may fall within time periods that are not captured by the trimester, such as a small window within the trimester or a window that straddles two trimesters.[42] Future analyses may consider applying a random selection method[42] to further explore whether there are susceptible periods for respiratory distress that fall within or overlap trimesters.

Although the MIREC cohort provided a rich, detailed data set in which to explore associations between air pollution and respiratory distress in neonates, our study has a few limitations. Compared with larger, administrative cohorts, our sample size did not provide sufficient power to fully examine potential effect modification and mediation by prematurity and fetal growth measures, such as LBW and SGA. Missing NO_2 monitoring data further limited our statistical power for NO_2 analyses and limited our ability to compare results for $PM_{2.5}$ and NO_2. However, sensitivity analyses suggest that $PM_{2.5}$ associations were similar when restricted to the smaller subset of participants with complete data for both NO_2 and $PM_{2.5}$. We classified exposure based on residential locations obtained at birth, which is a common approach in air pollution epidemiology. The lack of detailed residential history during pregnancy could result in potential exposure misclassification. However, $<8\%$ of MIREC participants moved during pregnancy, and sensitivity analyses suggest that results were similar when participants who moved were excluded from the analyses. Furthermore, previous studies comparing exposure classification based on a single location vs. detailed residential history found that this approach had a minimal impact on estimated associations between air pollution and birth outcomes,[81,82] providing some assurance in our results. Air pollution estimates were also linked to MIREC participants using FSAs—which vary in size—owing to privacy restrictions. To limit the potential exposure misclassification this might cause, we excluded participants residing in the largest FSAs from our analyses. Our analyses focused on exposure to ambient pollution, which can occur outdoors or via infiltration into the home. Although this is a common approach in air pollution health studies, we did not consider potential exposures due to indoor, occupational, recreational, and commuting sources.

Despite having detailed information about maternal and fetal health, we did not have access to neonatal breathing frequency or oxygen saturation, which would have provided an alternate metric for respiratory distress. We also were not able to adjust for maternal sedation during labor or history of oligohydramnios, which may have resulted in residual confounding. Finally, the MIREC Study population had older mothers, more White participants, higher income and education levels, and lower smoking prevalence compared with the general population, which may limit the generalizability of our results. Of note, multiple studies have shown racial/ethnic and socioeconomic disparities in air pollution exposure,[83–86] whereas, neonatal respiratory distress is more common among White newborns.[87] However, it is important to note that the overall incidence of respiratory distress ($\sim 7\%$–8%) and its underlying causes in our cohort were similar to those reported in the general population.[35] Nonetheless, further studies with diverse patient populations are needed to examine the impact of race/ethnicity and air pollution on neonatal respiratory distress.

Our study has several notable strengths. The MIREC cohort is a prospective, multisite cohort, recruited during early pregnancy, with detailed clinical, sociodemographic, and behavioral information. Thus, we were able to minimize spurious associations by controlling for both individual maternal characteristics and contextual socioeconomic variables. In addition, we used objective exposure and outcome measures to mitigate both recall and selection bias in our analysis. Finally, we conducted several sensitivity analyses to thoroughly understand the observed relationships and identify associations that were robust to model specification and statistical methods.

In summary, prenatal exposures to $PM_{2.5}$ were strongly associated with indicators of severe respiratory distress—including assisted ventilation and multiple clinical interventions, as well as the administration of systemic antibiotics—among term newborns in a multicity prospective pregnancy cohort. Our findings address a critical knowledge gap, and suggest that air pollution is a potentially modifiable risk factor for severe neonatal respiratory outcomes. This is significant because respiratory distress is a leading cause of neonatal morbidity and mortality worldwide,[36] and our results demonstrate adverse effects in areas with low ambient concentrations. These findings support the development and prioritization of public health and prenatal care strategies to increase awareness and minimize prenatal exposures to air pollution.

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